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All about epidermodysplasia verruciformis (EV): An inherited skin disorder

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ABSTRACT

Epidermodysplasia verruciformis (EV) is an uncommon genetic skin condition characterized by a high vulnerability to specific types of human papillomavirus (HPV), increasing the likelihood of non-melanoma skin cancer. The disorder is inherited in an autosomal recessive pattern, and certain families exhibit mutations in the TMC6 or TMC8 genes situated on chromosome 17q25.3. During childhood, individuals with EV frequently develop flat-topped, papular lesions that resemble verrucae planae on their limbs, reddish-brown plaques, or lesions resembling pityriasis versicolor on their neck, trunk, and face. In addition, more than half of patients may experience actinic keratoses and cutaneous malignancies during their twenties or thirties. Diagnosis of EV involves a skin biopsy to examine histological characteristics and detect HPV presence in a skin lesion. Additionally, there is an acquired form of EV observed in individuals with weakened immune systems. Although no definitive treatments exist for EV, patients are advised to rigorously practice sun protection measures to reduce the risk of developing non-melanoma skin cancer. Regular skin examinations throughout a patient›s lifetime are also recommended to detect precancerous skin lesions and early-stage cancer.

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Description of Epidermodysplasia verruciformis (EV)

EV is an uncommon hereditary skin disorder inherited in an autosomal recessive manner and associated with an increased vulnerability to certain types of human papillomavirus (HPV) infections [1]. Some cutaneous warts observed in EV patients are caused by chronic infection with specific β-HPV types [2, 3]. Affected individuals typically exhibit scattered lesions, including flat-topped papules resembling warts and macules resembling pityriasis versicolor, primarily on sun-exposed areas of the skin [4]. Moreover, more than 60% of EV patients develop various types of skin cancer, such as cutaneous squamous cell carcinoma (SCC), Bowen's disease (SCC in situ), basal cell carcinoma (BCC), and keratoacanthomas, at a young age [5, 6].

The development of cutaneous SCC in EV may be influenced by multiple factors, including direct DNA damage to keratinocytes due to ultraviolet (UV) radiation, inhibition of UVB-induced keratinocyte apoptosis by HPV, activation of HPV promoters by UVB, and local immunosuppression induced by UV exposure [7]. As a result, EV patients are unable to eliminate keratinocytes containing EV-HPV. The exact prevalence of EV is not well-established, but approximately 501 cases have been reported globally [8]. The precise pathogenesis of EV remains unclear; however, it is believed to involve genetic factors leading to selective immunodeficiency, EV-HPV infections, and exposure to UV radiation [9, 10].

Genetic Heterogeneity of Susceptibility to EV

Most families affected by EV inherit the disease through an autosomal recessive pattern. However, there have been rare reports of autosomal dominant inheritance and an X-linked variant known as EDVX [11-14]. EV1 and EV2 result from biallelic pathogenic variations in either TMC6 or TMC8 genes (also referred to as EVER1 and EVER2) situated on chromosome 17q25.3. These gene variants identified so far are categorized as loss-of-function variants, including nonsense, splice site, frameshift, exon deletion, or amino acid insertion, resulting in the production of non-functional proteins [15]. Additionally, EV3 is caused by variants in a third gene, CIB1, located on chromosome 15q26.1. Homozygous null variants in CIB1 have been found in 24 patients from six families [16]. Some individuals presenting with EV-like symptoms do not exhibit TMC6, TMC8, or CIB1 variations. Instead, variants in other genes involved in primary T cell or natural killer (NK) cell immunodeficiencies, such as RHOH (EV4), LCK, IL7 (EV5), MST1, CORO1A, and TGF-β, have been identified in a small number of patients who are susceptible to HPV types commonly observed in EV patients that suggests the presence of genetic heterogeneity in the disease [15, 17, 18].

Different Types of Human Papillomavirus in EV

Individuals with EV have an increased vulnerability to skin infections caused by specific types of HPV, primarily belonging to the β-HPV group [19]. These particular HPV types are typically considered non-pathogenic in the general population and do not integrate into the human genome or possess the E5 gene. Cutaneous SCCs in EV patients have been predominantly associated with EV-HPV types 5 and 8, which express the E6 and E7 oncoproteins [6]. However, the transforming potential of E6 and E7 proteins in most EV-HPVs is lower than that of high-risk genital α-HPVs (such as HPV16 and HPV18), suggesting that other factors, such as UV radiation, may play a role in the development of cutaneous SCC in EV patients [20, 21]. Moreover, various other HPV subtypes (such as 3, 9, 10, 12, 14, 15, 17, 19-25, 29, 36, 38, 46, 47, 49, and 50), as well as Merkel cell polyomaviruses, have been isolated from EV lesions [22-26]. Cutaneous cancers in EV patients have been found to harbor multiple HPV types, including β (1, 2, 3, 4, and 5), α (2, 4, and 8), γ (1, 2, 3, 4, and 5), and μ (1 and 2), with a higher frequency of β types [27]. A recent study reported the presence of 20 different HPV species, including three α-HPVs, 16 β-HPVs, and one γ-HPV, of which eight were newly identified in EV patients (β-HPV-37, -47, -80, -151, and -159; α-HPV-2 and -57; and γ-HPV-128) [28].

Acquired EV

An EV-like condition called acquired EV can manifest in immunocompromised individuals, including solid organ transplant recipients, HIV-infected individuals, and patients with severe combined immunodeficiency, albeit later in life [29-31]. The development of acquired EV may be associated with interleukin-2 (IL-2) receptor gamma chain deficiencies, abnormal downstream signaling in keratinocytes, or impaired natural killer (NK) cell development [32, 33]. Notably, single-nucleotide polymorphisms (SNPs) in traditional male circumcision (TMC) have been reported in HIV-infected patients but not in transplant patients, suggesting a potential role of SNPs in the development of acquired EV [34, 35]. The clinical and histopathological characteristics of acquired EV resemble those of inherited EV, and diagnosis is confirmed by the presence of β-HPV types 5 and 8 in skin lesions. Treatment for acquired EV involves reducing immunosuppression or addressing the underlying primary disease. Management and monitoring of skin lesions are similar to those of inherited EV. It is important to note that the clearance of EV-like lesions in HIV-associated acquired EV does not consistently correlate with improvements in cell counts following the initiation of antiretroviral therapy [35-37].

Pathology

EV lesions exhibit consistent histopathological characteristics, including a net-like basketball appearance of the stratum corneum, parakeratosis, and acanthosis [38]. Affected cell nuclei may appear condensed and surrounded by a clear ring, while the cytoplasm contains numerous round and basophilic granules. All individuals with EV show evidence of HPV types in the affected skin [38, 39]. A study investigating epidermal markers such as KRT1, KRT10, KRT14, KRT16, involucrin, filaggrin, and E-cadherin in EV lesions demonstrated decreased expression of K1 and K10, markers of mature and differentiated skin cells, as well as increased expression of K14, K16, and K4, which are not typically found in mature skin cells this suggests abnormal proliferation and differentiation of epidermal cells. The overexpression of these markers may be induced by the E7 gene of specific HPV types [40, 41].

Treatment

There is currently no known cure for EV, although specific therapies such as retinoids and interferons have shown some efficacy in treating the condition in select patients [42]. Additionally, topical imiquimod, photodynamic therapy, and topical fluorouracil have been used in some cases, but the results have been inconsistent [43-47]. It is important to note that recurrence is common once treatment is discontinued. Therefore, patients should be educated about the importance of sun protection to reduce the risk of developing actinic keratoses and non-melanoma skin cancer. Cryotherapy is recommended for treating actinic keratoses, Bowen's disease, and low-risk invasive cutaneous SCCs. Surgical excision is the preferred approach for SCCs with a higher risk of recurrence. It is advised to avoid radiotherapy for SCCs in EV patients, as it has been associated with aggressive tumor recurrence [48, 49].

Regular skin examinations are crucial for individuals with EV throughout their lives to detect and treat precancerous skin lesions and skin cancer at an early stage. Patients without malignant tumors should undergo annual check-ups by a dermatologist. However, those treated for invasive SCC may require more frequent skin examinations at three to six months, as recurrences or metastases often occur within two to five years after therapy [50].

EV is a rare, genetically heterogeneous skin disorder primarily inherited in an autosomal recessive manner, characterized by increased susceptibility to specific β-HPV types and a markedly elevated risk of non-melanoma skin cancers. Mutations in genes such as TMC6, TMC8, and CIB1, as well as other immune-related genes, contribute to its pathogenesis by impairing the immune response to HPV. Clinically, EV manifests in childhood with wart-like or pityriasis versicolor-like skin lesions, which often progress to premalignant or malignant lesions in early adulthood, particularly under UV exposure. Acquired forms of EV may also develop in immunocompromised individuals, mirroring the clinical and histological features of the inherited type. Although there is no definitive cure, current management focuses on lesion-specific therapies, rigorous photoprotection, and lifelong dermatologic surveillance to reduce the risk of malignancy and enable early detection and treatment of skin cancers.

Authors' contributions

SN, NF, and SSM conceived the idea and scope of the review. The literature search, data collection, and analysis were performed by SN, NF, AK, MM, and SSM. The manuscript was written and critically revised by SN, NF, and SSM. All authors read and approved the final version of the manuscript.

Conflict of Interest

The author reported no potential conflict of interest.

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